biopsy is that we lack adequate therapy for each type of renal disease and that the 'informational content' of renal biopsies is judged by the physician's opinion on treatment and prognosis and often not on the basis of randomized controlled studies. An important example of this point is the management of adults with a nephrotic syndrome due to a focal segmental glomerulosclerosis. We have reported that the nephrotic syndrome in patients with the glomerular tip variant of FSGS and also what we have called early classical focal glomerulosclerosis does respond to steroids and immunosuppressants and that with this treatment progression to renal failure is reduced [14]. It is argued that even though in these patients a renal biopsy changed management, in the absence of randomized controlled studies of sufficient power to indicate the effectiveness of the proposed treatment, then the biopsy would in itself have been useless.

Conclusions

The ISKDC guidelines for the initial treatment of children with a nephrotic syndrome with steroids as outlined above remain valid. We would argue that in adults with an idiopathic nephrotic syndrome, blind treatment with steroids means unnecessary treatment of a large proportion of patients (approaching 70%) with a potentially toxic drug. It also means that no assessment would be available of the type of glomerulonephritis or an estimate of the likelihood of a response to treatment and of the prognosis for long term renal function. This differs substantially depending on the histology. In skilled hands the dangers of renal biopsy are small and outweighed by those of unnecessary steroid treatment. Nevertheless the arguments for blind treatment of the nephrotic syndrome with steroids emphasize the paucity of effective treatment for the nephrotic syndrome in adults and the need for controlled studies in these disorders.

References


Does the modality of haemodialysis treatment affect lipoprotein composition?

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Why is lipoprotein clearance decreased in chronic renal failure?

Many haemodialysis patients suffer from cardiovascular morbidity and mortality. Usually, several recognized risk factors are present, i.e. hypertension, left ventricular hypertrophy and dyslipidaemia. The characteristic lipid abnormalities consist of a moderate hypertriglyceridaemia, increased lipoprotein (a), relatively normal total cholesterol, but decreased HDL cholesterol. Changes can be detected before the patient has reached end-stage renal failure, and they become more pronounced when renal failure progresses and

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AGEs are reduced from predialysis to postdialysis by end-stage renal disease, with or without diabetes mellitus [15]. AGEs contribute to collagen predialysis levels were significantly reduced in patients high-flux dialysis but not by conventional dialysis, and dialysis with or without diabetes exhibit high circulating levels of protein- and lipid-bound AGEs [15]. Such changes invariably lead to a decreased clearance of these particles via the apo B/E receptors [6–8], resulting in a decreased fractional catabolic rate [9] and increased uptake by scavenger receptors on arterial smooth muscle cells, a process which may play an important role in atherogenesis [6,7].

**Does high-flux haemodialysis affect lipid patterns and LPL?**

Two separate lines of evidence indicate that high-flux (HF) haemodialysis may improve lipid profiles. The first concerns lipolysis. A number of studies report a 30–50% decrease in plasma triglycerides in patients on HF dialysis [10–13]. Although this was first ascribed to an increase in LPL activity [12], we could not find a difference between either basal LPL activity or the acute dialysis-related (heparin-induced) increase in LPL activity for the two membranes [13]. This does not exclude the possibility that LPL in situ on the endothelial wall may be more effective because the removal of its inhibitor apolipoprotein CIII appears to be more effective with HF haemodialysis [14].

**Are advanced glycation end-products (AGE) involved?**

Recently, however, information has become available that indicates that HF-haemodialysis, beside its effect on triglycerides, also reduces levels of apo B that are modified by advanced glycation end-products (AGEs) (Helen Vlassara, 13th Congress of International Society of Nephrology, Madrid, 1995). Patients on dialysis with or without diabetes exhibit high circulating levels of protein- and lipid-bound AGES [15]. AGES associated with LDL (both in the apo B and phospholipid moiety) are increased in patients with end-stage renal disease, with or without diabetes mellitus [7]. Macromolecules such as lipoproteins are not removed by dialysis, however low-molecular-weight AGES are reduced from predialysis to postdialysis by high-flux dialysis but not by conventional dialysis, and predialysis levels were significantly reduced in patients on high-flux dialysis [15]. AGES contribute to collagen crosslinking, occupy specific receptors that promote cytokine and tissue factor release, increase vascular permeability, can chemically inactivate ('quench') nitric oxide and may play a role in initiating lipid oxidation. Thus AGES probably play a role in the multiorgan complications of diabetes mellitus, but also in normal aging and renal failure.

The question that we are now confronted with is obvious. Are these separate effects of HF haemodialysis or are we looking at two sides of the same coin? We would like to propose that HF haemodialysis by lowering the levels of low-molecular-weight AGES is reducing AGE modification of triglyceride-rich lipoproteins, namely VLDL and IDL. Consequently, more VLDL and IDL will be cleared by the hepatic apo B/E receptors, thus reducing both the accumulation of plasma triglycerides and the generation of AGE-modified LDL. Obviously this proposal is not supported by direct evidence, and a number of questions must be addressed.

Are VLDL and IDL also AGE modified in patients with chronic renal failure? If this is the case; does HF haemodialysis also reduce AGE modification of VLDL and IDL? If low-molecular-weight AGES are involved in the chemical modification of lipoproteins, administration of these molecules to animals expressing apo B/E receptors such as rabbits, should increase triglyceride levels and reduce the clearance of LDL. Alternatively, low molecular weight AGES may reduce LPL activity in situ.

**HF haemodialysis—an approach to treat dyslipidaemia in dialysis patients?**

Irrespective of the mechanisms involved, it is clear that HF haemodialysis has an important effect on lipoprotein composition, both because of the triglyceride-lowering effect and because it decreases the levels of atherogenic chemically modified lipoproteins. HF haemodialysis is not burdened with the sometimes serious side-effects of lipid-lowering medication. It is therefore an attractive first-line approach to dyslipidaemia in patients on chronic haemodialysis.

**References**

Dynamic tests of parathyroid gland function have been used by several groups of investigators to evaluate parathyroid hormone (PTH) secretion in patients with various disorders of mineral metabolism including chronic renal failure [1–7]. Elsewhere in this issue, Malberti and colleagues describe changes in the pattern of PTH release in patients with secondary hyperparathyroidism [7,12]. These assessment models were used to examine the regulation of PTH secretion in secondary hyperparathyroidism. Specifically, calcitriol is thought to lower the set point for calcium-regulated PTH release and that the set point differs in various types of renal osteodystrophy [13,14]; these methodological differences warrant further consideration.

Mayer and co-workers originally described the inverse sigmoidal relationship between the concentration of ionized calcium in serum and the serum level of parathyroid hormone (PTH) across the physiological range of ionized calcium values in studies in the calf [15]. Subsequent work by Brown and associates using dispersed parathyroid cells obtained from patients with parathyroid adenomas or parathyroid gland hyperplasia documented a similar relationship between the amount of PTH released in vitro and the calcium level in tissue culture media [2,16–19]. Because calcium is the major regulator of PTH release, curve-fitting models that had been applied to the assessment of other physiological functions with non-linear properties such as enzyme kinetics and ligand-receptor interactions were used to examine the regulation of PTH release by calcium in vitro [2,20]. These assessments sought to better characterize the components of PTH secretion at the cellular level and to determine whether the control of PTH secretion by calcium differed in various disease states [6]; they also form the basis for in-vivo studies of the dynamics of PTH secretion in patients with secondary hyperparathyroidism and other disorders of mineral metabolism.

As depicted by the following equation, the model employed by Brown and colleagues provides estimates of the amount of PTH (Y) released at any concentration of ionized calcium (X) using four parameters derived by direct measurement: A, the maximum PTH value observed at reduced ionized calcium levels; D, the minimum PTH value observed at high concentra-